# A Review of the Lesions in Shipping Fever of Cattle

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SUMMARY

A review of literature concerning the information published on the macroscopic and microscopic lung lesions in "shipping fever" of cattle is presented as reported in naturally occurring cases as well as the experimental disease.

RÉSUMÉ

**Une revue des lésions de la fièvre du transport des bovins**

Cet article contient une revue de la littérature concernant les informations relatives aux lésions pulmonaires macroscopiques et microscopiques des cas naturels et expérimentaux de fièvre du transport, chez les bovins.

## INTRODUCTION

In spite of large amounts of time and effort expended in understanding various etiological, epidemiological and immunological aspects of the disease, bovine pneumonic pasteurellosis (shipping fever) still remains as one of the most important causes of sickness and mortality in cattle. The extent of the economic losses sustained has been indicated by several authors (27,30). The annual loss attributed to this disease in the United States alone in 1954 has been estimated at 25 million dollars, excluding the cost of treatment or preventive measures (43). The total economic loss at present would probably be much greater.

Attempts to understand the disease fully have been generally unsuccessful. The disease has been studied extensively in natural cases and experimentally infected animals (6, 9, 11, 13, 14, 16, 18, 22, 28, 37, 39, 40, 48, 49, 52). Subsequent to the work of Collier and associates, which investigated 13 epizootics of "shipping fever" over a period of three years, the awareness of the role of Pasteurellae in this disease increased gradually and was emphasized in a symposium on the respiratory disease complex of cattle in 1967 (11, 46).

Although the terminal stages of the disease are well recognized and easily differentiated from other forms of pneumonias (3), the pathogenesis of the early stages has not been investigated (29) nor is the role of etiological agents and stress factors in causing the disease fully understood (3). Thus, there is no unifying concept for the epizootiology and pathogenesis of "shipping fever" although many hypotheses have been postulated (18, 29, 49, 52). Unless all the contributory aspects are investigated, and the pathogenesis is known, control of pneumonic pasteurellosis or "shipping fever" will not be completely effective.

An exhaustive search in the literature revealed few detailed descriptions of the lesions in natural cases of pneumonic pasteurellosis of cattle. Since these accounts pertained to the examination of fatal cases, some descriptions of the lesions were consistent with terminal stages of the disease. Few workers have attempted to elucidate the earlier events that may be occurring in natural cases under field conditions. The objective of this paper is to review the information published in literature relating to the gross and microscopic lung lesions in "shipping fever" of cattle. The lesions in naturally occurring cases will be described first, followed by those produced in the experimental disease. Review of the descriptions of lesions in enzootic pneumonia of calves (32, 47) is not included.

## TERMINOLOGY AND BACTERIOLOGY

The term "shipping fever" has probably been in use for over six hundred years. Literature records Rusius as saying "Great losses occurred among the war horses of Rome in the year 1301" (51). In horses, the term was in general use to encompass a large variety of ailments including influenza, strangles, pleuropneumonia, epizootic cellulitis, pink eye, catarrhal fever and typhoid pneumonia. It was not until the turn of this century that "shipping fever complex" was recognized as having three distinct etiological entities namely strangles, influenza and contagious pneumonia (45).

With reference to diseases of cattle, the same term was in frequent use in the early 1900s (22) which appears to have been the onset of an era of confusion. For the following 60 years the terms "shipping fever", "transit fever", "stockyard's pneumonia", "exposure disease", "transport fever" and "haemorrhagic septicemia" in their various forms, eluded clear definition and continued to mislead investigators. Only in the past ten years has the term "pneumonic pasteurellosis" attained recognition as a distinct disease entity of the so-called "shipping fever complex" (46). The confusion, though, surrounding the many etiological and epidemiological aspects of the disease still remains (40, 49).

The controversy surrounding the role of various etiological agents and stress in causing penumonic pasteurellosis, has been equally ambiguous. Theodore Kitt in 1885 first described the causative agent, which he called *Bacterium bipolare multocidum*, later changed to *Bacillus bovisepticus* by Flugge in 1896. It was not until 1900 that Lignieres proposed the name *Pasteurella* for the genus and the respective name of the species of animals to indicate pathogenicity hence, *Pasteurella boviseptica* (34). Tosenbusch and Merchant proposed the name *Pasteu-*

*rella multocida* in 1939, to replace *Pasteurella septica* of Topley and Wilson (1936), which obtained universal acceptance. *Bacillus bovisepticus* previously in group I of Jones (1921) were given the name *Pasteurella hemolytica* by Newsom and Cross in 1932 and this has also been widely accepted (7, 10). Serological classification and association of various serotypes of *P. multocida* and *P. hemolytica*, with specific disease entities in animals has since come a long way, in terms of geographical distribution, pathogenicity, host and age susceptibility. As a result of the work of Roberts, Carter, Namioka and Bruner, specific serotypes of *P. multocida* and their association with specific diseases have attained universal acceptance (7, 8, 45). Similarly, subsequent to the efforts by Smith, Carter, Biberstein and Thompson, the serological classification proposed for *P. hemolytica* has obtained worldwide recognition (7). Although the significance of *P. hemolytica* in pneumonic pasteurellosis of cattle was generally accepted, it was not until 1960 when Collier and associates succeeded in producing a severe clinical disease in calves, that the attention shifted to this organism (12). This newly aroused interest was further stimulated by the demonstration of the possible role of *P. hemolytica* in 12 natural epizootics of "shipping fever" (11). Collier (11) isolated the organism in pure culture from the pneumonic lung tissues of weanling Hereford calves in the above epizootics in Colorado. The mounting evidence since, led Jubb and Kennedy (29) to categorically state that *P. hemolytica* serotype 1 of Biberstein and Thompson "is associated to the virtual exclusion of other serotypes with pneumonic pasteurellosis (shipping fever) of cattle" (29). If *P. multocida* can cause similar lesions there is little if any reported evidence to support its ability to do so. The same applies to mycoplasma species.

## MACROSCOPIC LESIONS

Pneumonic pasteurellosis in cattle, as recognized today, is an acute fulminating lobar fibrinous pneumonia (29). While reports of the occurrence of the disease in literature are numerous, few workers have devoted attention to the aspects of lung lesions in any detail. The descriptions of gross findings have been sparse and often inaccurate, in relation to the extent of involvement and severity.

*Natural Cases*

Hardenbergh and Boerner (22) referred to anterior lobes of the lungs as being the site of the lesion. Hepburn (25) found the lesion in majority of the cases as being confined to the apical lobes, although sometimes both apical and cardiac lobes were found affected, while Palotay (35) described consolidation of one-third or more of the lung in 96% of the 47 necropsies without reference to the lobes where the lesion was observed. During necropsy examination in 57 recently shipped Hereford cattle from feedlots, Graham (18) found 29.9% with consolidation of one-third or less of the lung, 58% with one-third to two-third and 8.8% of the cases exhibited consolidation in over two-thirds of the lung. Carter (6) examined 35 lungs from recently shipped cattle exhibiting signs of "shipping fever". He stated "the amount of lung tissue involved in the pathological process varied from cases in which only the anterior and cardiac lobes were severely affected to those in which all lobes were involved". According to Palotay and Newhall (37) a confluent pneumonia affected the anteroventral two-thirds of both lungs in 54 calves (5.6%) which died out of 990 newly weaned calves. Tweed and Edington (52) found, in seven bovine lungs they examined, that the pneumonic areas were usually confined to the lower borders of the lungs, but the whole of the apical lobe was commonly involved. To Schiefer *et al* (40) a third of the lungs dorsal to a horizontal plane passing through the thoracic inlet looked normal, whereas the lower two thirds were enlarged, firm, heavy and of flesh-like consistency (40). Most other descriptions of the location of the lung lesions, however, were vague and imprecise. In their description of the natural disease in recently shipped cattle, Gale *et al* (15) stated simply that the lungs had severe pneumonia. In 22 (37.3%) pleuropneumonic cases examined in a group of 59 calves, lungs showed areas of fibrinous consolidation (34). Other reports made general reference to the lesion as pneumonia alone (4) croupous pneumonia (41, 42) and lobar pneumonia (38) without any indication of the location and extent of involvement.

Acute fibrinous or serofibrinous pleuritis was a common finding in most cases of pneumonic pasteurellosis (29). The occurrence of this feature has been variously stated by many workers. Severe fibrinous pleuritis was considered to be the most impressive lesion (37). Cattle with fibrinous pleuropneumonia had grossly bilateral fibrinous pleuritis with either removable sheets of fibrin or firmly attached strands and networks of fibrin on the visceral and parietal surfaces (40). The amount of fibrinous exudate deposited on the pleural surface was found to be heavy (41) or variable (6). Pickering (38) observed that the extent of the deposits of fibrin on the pleura depended on the degree of pleurisy present. In addition to fibrinous pleuritis, Norrung (34) observed that often serofibrinous pericarditis was present. Thickening of the pleura which usually had a greyish fibrinous deposit on the surface (52) was a common finding. Of 47 cases examined, pleuritis was present in 77% of the cases (35) while 80.7% of the 57 animals examined revealed the same lesion in another study (18). In some instances, mention of the pleura was not made (4, 15, 42) and at least in one instance, it was found to be normal or often the surface of the lungs was "petechiated or ecchymotic" (22).

Several workers have observed the presence of fluid in the pleural cavity (52). Palotay and Newhall (37) stated that the abundant yellowish pleural fluid coagulated rapidly on exposure to air. Most descriptions, however made no mention of the presence or absence of fluid, and Hepburn (25) stated that the presence of fluid exudate in the thoracic cavity was never observed.

The data relating to the interlobular septa were generally in agreement with different observers. Tweed and Edington (52) stated that the interlobular tissue was very marked and distended due chiefly to the presence of coagulated exudate. Thickening of the interlobular septa with fibrin (18) and infiltration with serum (22) which in some instances extended out under the vis-

ceral pleura (6) were common observations, although in one instance interstitial edema in the lungs was never observed (38).

The bronchi were hyperemic and partly filled with blood, pus and mucus (40). Graham (18) observed blood clots in the bronchi in 17 (29.8%), and pus in two (3.5%) of 57 animals examined. The mucous membrane lining the bronchi was inflamed and showed a blood stained exudate mixed with air (52) and serum could be expressed from the bronchioles (6). In other cases, the bronchial tubes contained frothy mucus and the lining membrane was thickened (22) while accumulation of croupous exudate in the bronchi was observed in some cases (41).

There appears to be a remarkable consistency in the observations relating to the pattern of lobular consolidation, and the similarity to the appearance of the lung to some cases of contagious pleuropneumonia of cattle (34, 40, 41, 52). Reference is generally made to the so-called distinct areas of "hepatisation" (38, 41) with a "lobular patch here and there" throughout the lung substance (25). The affected anterior lobes were dark-red and pneumonia of the lobular type was a very constant complication (22). Schiefer *et al* (40) found that lobules in the affected ventral areas were either red, grey or black. Norrung (34) mentioned areas of fibrinous consolidation in the lungs. Pneumonic areas were clearly demarcated from the nonpneumonic areas, the latter were pink and spongy while the former were dark-red and "hepatised" (52).

Carter (6) stated that, in the affected part of the lobe, some lobules were congested and edematous, and some were turgid with blood suggesting incipient infarction, but the majority of the lobules were consolidated. They were red to grey. Distinct stages of pneumonia were present in the same lung, and healthy lobules appeared between the consolidated ones (52). Similar observation was made by Carter (6) when he observed that the pneumonic process was patchy in distribution with normal appearing air-containing lobules outstanding in the affected areas.

Examination of cut (or cross) section of the consolidated lobes was reported in several cases. Hepburn (25) found that this gave a constant appearance of a lobar pneumonia. Carter (6) found that on cut section, the terminal bronchioles were outlined to present a "clover leaf" effect, however very little material could be pressed from the affected lobules. On cross sections through altered lobules, Schiefer *et al* (40) found airless lobules were alternately either dark-red or grey-white and yellow fibrin in interstitial septa separated such lobules. The cut surface of the pneumonic lobes showed, to Tweed and Edington (52), a striking picture of dark-red consolidated tissue intersected by thickened white septa, giving the diseased lung a mottled appearance. This surface was moist and exuded serous fluid. In more chronic cases, grey circular dry areas could be seen amidst the solid tissue (52). These same areas of coagulation necrosis were described in other words 12 years previously by Hardenbergh and Boerner (22) when stating that cross section of the dark-red consolidated lobes, revealed numerous small cavities containing yellowish cheesy pus. Jubb and Kennedy (29) stated that necrosis of parts or all of lobules is common and with respect to its pathogenesis, there is often difficulty in deciding how much to attribute to direct microbial action on the parenchyma and how much to vascular injury.

In the course of the review, some literature was found where apparent inaccuracies existed. Langham *et al* (31) described an anteroventral purulent bronchopneumonia rather than fibrinous pneumonia associated with pneumonic pasteurellosis. Gale *et al* (15) described the lungs taken from a recently shipped Hereford steer, as having severe pneumonia. The accompanying photograph of the lungs reveals an obvious anteroventral bronchopneumonia. Description of gross lesions in the lungs were sparse; pneumonic lesions were present in lower parts of all lobes (15). Mention was made of lung lesions being usually patchy; showing areas of red and grey consolidation, and often zones between consolidated areas and normal lung tissue were markedly congested, and further that atelectasis and emphysema were often observed (31). Descriptions and photographs of histopathological lesions indicate a purulent bronchopneumonia.

Lesions comparable to those described for natural cases of "shipping fever" (22, 29, 40, 52) have been observed in other diseases caused by experimental infection of different etiological agents (2, 44) as well as in some natural cases of contagious bovine pleuropneumonia (5).

*Experimental Cases*

Various authors have described attempts at reproducing "shipping fever" by using combinations of stress, contact exposure and single or multiple agents in experimental infections (19, 24, 28, 39, 53). The evaluation of the degree and nature of lung lesions produced in successful trials were either not given (19) or appears to be inconsistent with those of pneumonic pasteurellosis (20) while in other cases attempts were unsuccessful (6, 16, 23, 26). However, descriptions of consistent lesions of fibrinous pneumonia were encountered in some successful attempts (13, 28, 36).

The description and photograph of gross lung lesions in a calf (36) produced by experimental intratracheal infection of suspension of crude lung material obtained from calves that died from pneumonic pasteurellosis, were consistent with those of "shipping fever". There appears to be an obvious severe fibrinous pneumonia in anteroventral third of the lungs. Although a detailed description is not given, the photograph of a cross section of the pneumonic lobe from another calf (36) given an intratracheal inoculation of *P. hemolytica* and sporadic bovine encephalomyelitis "virus", exhibits a diffuse fibrinous consolidation, septal dissection, and a lobular pleuropneumonia, consistent with that of "shipping fever". The presence of various groups of lobules in different phases of the reaction shows clearly as marbled lung (29), although areas of necrosis in these lobules cannot be discerned from the photograph.

Other accounts of gross lesions in experimental animals were less clear. Gale *et al* (15) used materials from a Hereford steer referred to above, to reproduce "shipping fever" by experimental infection in healthy calves. A photograph of the lung and the description of the lesions is vague, and

generally mention is made of areas of severe pneumonia and consolidation in ventral portions of the anterior lobes with dark red and white foci scattered under the pleura (15). Similar apparent discrepancies existed in the account of Hamdy *et al* (20). Pneumonia was produced in a calf after exposure with *Pasteurella* spp., parainfluenza-3 virus (PI-3), psittacosis-lymphogranuloma venereum agent and physical stress. Although the lesion is described as fibrinous pneumonia, fibrinous pericarditis and pleuritis, the photograph of the lung exhibits severe anteroventral bronchopneumonia. In both of the above investigations (15, 20) these discrepancies are further evident from histological descriptions (see below). Heddlestone *et al* (24) produced pneumonia in calves by exposing them to animals showing clinical signs of "shipping fever". However, the description of the gross lesions of the lungs in experimental calves, mentioned pneumonia in which inflammation and purulent exudate were seen in all lobes. The corresponding histological description (see below) clearly showed that the pneumonia produced was not fibrinous, but was purulent bronchopneumonia. Classical lesions of acute fibrinous pneumonia have been produced by exposure to parainfluenza-3 virus and *P. hemolytica* (1) or *P. hemolytica* alone (13). Descriptions of these gross lesions produced by experimental infection appear to be consistent with those of "shipping fever". Severe and extensive consolidation of apical, cardiac and diaphragmatic lobes, exhibiting dark-red, very firm lobules, with separation of interlobular septa by fibrin, and fibrinous pleuritis were produced as early as three days following intratracheal inoculation of *P. hemolytica* in calves (13). Baldwin *et al* (1) produced "most severe pneumonic lesions" in calves exposed to both parainfluenza-3 virus and *P.hemolytica.* Lesions described are consolidation of 50% or more of the lungs, a few normal areas containing pneumonic patches and exudate in bronchi which yielded cultures of pure *P. hemolytica.* Lesions consistent with acute fibrinous pneumonia have been produced in 16 calves, exposed to an aerosol of infectious bovine rhinotracheitis (IBR) virus followed four days later by aerosol exposure containing *P. hemolytica* type 1 organisms (28). The lesions described are "lobar pneumonia" in 11 infected calves and pneumonia involving one or both lungs in four calves. In two of these calves, both apical, both cardiac and more than half of both diaphragmatic lobes of lungs were consolidated. These authors also described the presence of 2 L of straw colored thoracic fluid and up to 5 mm thick layers of fibrin deposited on the pericardial sac and visceral pleura of the lungs.

At this juncture in the review, it is appropriate to mention in brief, some aspects of gross lesions in the lungs, bearing some resemblance to "shipping fever", produced by natural and experimental infection with other agents. Bygrave *et al* (5) have described typical acute lesions in the lungs of cattle, sick from contagious bovine pleuropneumonia caused by *Mycoplasma mycoides* var. *mycoides.* All lobes of the affected lungs had red consolidation, which was uniform over large areas. Pronounced hemorrhage masked the interlobular septal involvement and produced a "marbled" appearance. On cut section, the lung surface exuded large quantities of serous lymphatic fluid from the distended interlobular lymphatics and the bronchioles. Shope (43) produced diffuse fibrinous pneumonia in pigs following experimental infection with *Haemophilus parahemolyticus (H. pleuropneumoniae).* These pneumonic lobes were purplish red; "cut almost like liver" and interlobular septa were widened by bloody gelatinous fluid. Strands of loosely adherent fibrin and yellowish exudate overlaid pneumonic areas of the lungs (44). Photographs of the subgross sections of the lung lesions clearly shows "bizzare designs, and irregularly shaped areas with discretely outlined margins" not unlike those produced by experimental *P. hemolytica* infection in calves (13). Hani *et al* (21) have described confluent, lobular to lobar, black-red to grey-red elevated foci of consolidation and serofibrinous pleuritis in pigs with natural and experimental infection with *H. parahemolyticus.* Photographs of gross lesions in the lobes, reveal numerous pale irregular areas of necrosis comparable to those of calves (21). Baskerville and Dow (2) have described diffuse anteroventral consolidation of lungs, following experimental infection with *Salmonella cholerae-suis* in pigs. The affected regions were very firm and dark-red to greyish purple. Yellow-grey areas projected above the contours of the surrounding pneumonic tissues. According to Baskerville and Dow (2) these areas, on cut section, "resembled abscesses", and they were clearly demarcated from the healthier surrounding tissue. The photomicrograph from this lesion bears striking resemblance to areas of necrosis produced in calves (13) as elaborated below.

## MICROSCOPIC LESIONS

The histological lesions in lungs of cattle with pneumonic pasteurellosis are characteristically those of acute fibrinous pneumonia and pleuritis (29). Depending on the stage when examined, features commonly observed are predominantly fibrinocellular exudate comprising mononuclear cells, edema, bronchiolitis and characteristic swirly dark macrophages in alveoli and alveolar ducts. In terminal stages, multifocal areas of coagulation necrosis are present in the parenchyma of the affected lobes (13, 46).

While descriptions of gross lesions encountered in natural and experimental cases of "shipping fever" have been usually referred to in general terms, there are few reports of detailed histological investigations in the literature. Descriptions of microscopic lesions have been either very sparse, or in some cases reveal evidence that casts doubt as to the authenticity of the lesion in question.

### *Natural Cases*

Usually there is no mention of the appearance of the pleural surface of the lung microscopically. A fibrinous pleuritis was present in some cases (52). These authors also observed thickening of interlobular septa which was attributed to coagulated material filling up septal lymphatics and blood vessels. Graham (18) examined lesions microscopically in lungs from 48 animals. The interlobular septa were fibrinous in 47 (97.9%), emphysematous in 27 (56.3%), edematous in 38 (83.3%), and exhibited fibrosis in five

(10.4%) animals. In 39 (81.3%) of the animals, there was thrombosis of the septal lymphatics. Carter (6) stated that septal interstitial tissue contained considerable amounts of fibrin, and lymphatics often were occluded by fibrinous plugs. According to Schiefer *et al* (40) extreme dilation of interstitial septa by thrombosed lymph vessels was one of the outstanding features. The lobular distribution of the lesion appeared to be characteristic (6) and the lobular vessels and lymphatics getting filled with coagulated material resulted in high fluid content in the lobules (52).

Most bronchi and bronchioles in lobules surrounded by thrombosed lymphatic vessels in the interstitium showed little or no inflammatory changes in the mucosa, but neutrophils, cellular debris and sometimes fibrin frequently were seen in the lumina (40). The terminal bronchioles in the diseased lobules showed varying grades of inflammation, were often plugged with "pus cells and their disintegrated products" (52), while Carter (6) noted that terminal bronchioles were filled with an extremely cellular exudate consisting chiefly of mononuclear cells in varying stages of degeneration. Graham (18) found bronchiolitis in up to 42 (87.5%) of the 48 animals examined. In a large number of cases, the epithelial lining of the bronchi was swollen (64.6%) and desquamated (83.3%).

Tweed and Edington (52) described so-called early changes in alveolar walls when capillaries were congested with occasional hemorrhage into alveoli. There was exudation of serum into alveolar spaces, and desquamation of lining alveolar epithelial cells. Carter (6) observed in areas adjacent to the lobules with exudate, that alveoli contained fibrinous exudate in which there were numerous neutrophils, areas of compensatory emphysema and some normal appearing alveoli.

In the affected lobules, the alveoli were filled with an extremely cellular exudate consisting of chiefly mononuclear cells (6) polymorphonuclear and "catarrhal cells" (52). Generally in these natural cases, large areas of hemorrhage were found in some sections (6). Schiefer *et al* (40) found dark cells appeared either as round, large macrophages with pale eosinophilic cytoplasm, or as fusiform cells packed into alveolar spaces and alveolar ducts. The description of Graham (18) is somewhat confusing. In over 68% of the 48 animals examined histologically, "red hepatisation", "grey hepatisation", hemorrhage, atelectasis and emphysema in the alveoli, were noted. In less than 36% of the cases, resolution, organization of fibrin, infarcts, "gangrenes" and abscesses were recorded (18). All these terms are used very vaguely and their meaning is difficult to discern.

In the few descriptions of microscopic lesions in natural cases, rarely is there specific mention of areas of necrosis. Schiefer *et al* (40) found, as an outstanding feature, coagulation necrosis in lobular fashion and distinct accumulations of dark cells that were arranged along thrombosed lymph vessels, filled alveolar spaces or were at the edge of necrotic areas, Tweed and Edington (52) stated that in cases which recover the pneumonic lung may undergo complete restoration, but occasionally "chronic abscess formation" may occur.

Reference to changes in the blood vessels were few. To Schiefer *et al* (40) many blood vessels, both arterial and venous, as well as septal capillaries contained homogenous blood clots. Graham (18) found pulmonary vascular thrombosis in 22 (45.8%) of the 48 animals examined.

Gale *et al* (15) described a natural case of "shipping fever". Their description contains marked apparent discrepancies. The predominant exudate in bronchi and alveoli was polymorphonuclear. Fibrin was not present. Bronchiolitis and peribronchiolitis with peribronchiolar cuffing of inflammatory cells were prominent features. Mention is made of scattered foci of early suppuration in the lobular parenchyma. The photomicrographs are those of acute purulent bronchopneumonia.

Langham *et al* (31) described the exudate as primarily polymorphonuclear leukocytes and "putrid exudate". Bronchial epithelium was necrotic, and peribronchiolar cuffs were described. Obliterative bronchiolitis and atelectasis was mentioned in relation to purulent exudate in lumen of bronchioles. Also described was necrotizing bronchitis and bronchiectasis and purulent exudate in bronchial lumina. The photomicrographs confirm that these cases are essentially subacute and chronic cases of purulent bronchopneumonia, not acute fibrinous pneumonia, associated with pneumonic pasteurellosis.

*Experimental Cases*

Many attempts to reproduce "shipping fever" in normal calves by experimental infection of morbid materials and cultures recovered from pneumonic calves, were failures (6, 16). In some successful attempts (1, 36, 37, 42) only the macroscopic lesions in the lungs were described. Few reports of detailed histological investigations in experimentally induced cases were found. Some of these were not *bona fide* acute fibrinous pneumonias. The lack of adequate detailed microscopic descriptions of the lesion, therefore does not allow comparison with field cases (29).

Gale *et al* (15) attempted to reproduce "shipping fever" in susceptible animals, by exposing them to materials obtained from natural cases, using several routes. The gross lesions produced were found to be those of purulent bronchopneumonia (see above). The description of the microscopic lesions further substantiates this conclusion. Bronchiolitis and peribronchiolitis with primarily a neutrophilic exudate are described as prominent changes in the lungs. The inflammation was found extending through the bronchiolar walls and masses of neutrophils and monocytes formed heavy borders around the bronchioles. In the larger bronchioles, epithelial hyperplasia was present. The photomicrographs of the lesion described is clear evidence of suppurative bronchopneumonia with predominantly a polymorphonuclear exudate (15).

Heddlestone *et al* (24) attempted to transmit "shipping fever" in susceptible animals by placing them with sick calves. The gross lesions produced were consistent with purulent bronchopneumonia (see above). Their histological descriptions "showed characteristic lesions of purulent lobular pneumonia". The larger bronchioles were intact and contained a few leukocytes but in other areas the smaller bronchioles were almost obliterated

by the cell infiltrates. In several sections the polymorphonuclear leukocytes were actively migrating through disrupted and degenerate bronchiolar walls (24).

Hamdy *et al* (19) used combinations of various bacterial and viral agents and stress, in their attempts at experimental transmission of "shipping fever". Gross lesions in the lungs suggested bronchopneumonia (see above). The descriptions of microscopic lesions and photomicrographs illustrating them, do not show an acute fibrinous pneumonia with characteristic macrophagic exudate. Reference was made to suppurative bronchiolitis in two calves. Another calf had "purulent bronchitis and bronchiolitis with many neutrophils and lymphocytes". Also observed was "a marked increase in lymphoid tissue around the bronchioles in areas where pneumonia was not present" (20).

Observations concerning the lesion in the alveoli and lobules were also consistent with purulent pneumonia (15, 20, 24). Gale *et al* (15) described inflammatory activity from the bronchioles extending into the parenchyma causing atelectasis, thickening of alveolar walls and partial filling of alveoli with neutrophils and debris. The inflammatory reaction centered around a few bronchioles and appeared to be spreading from this central point. In other instances, the inflammatory reaction affected whole lobules and complete atelectasis had developed. Heddlestone *et al* (24) found most lobules were "either diffusely infiltrated by polymorphonuclear cells or entirely free of cell infiltrates" and in others, the neutrophils were "localized to discrete foci within lobules". Hamdy *et al* (19) described the alveolar spaces in several calves as being affected by hemorrhage and edema, containing lymphocytes, few neutrophils, fibrin and many large mononuclear cells. The alveolar walls were hyperemic, fragmented and thickened with macrophages, lymphocytes and neutrophils.

Microscopic lesions described in pneumonia in calves induced by experimental infection of *P. hemolytica* (13) compared very well with those of acute fibrinous pneumonia encountered in natural cases of "shipping fever" (29). In early stages, varying degrees of atelectasis and bronchiolitis are described, as well as infiltration of neutrophils and accumulation of macrophages and fibrin in alveolar spaces, especially around bronchioles (13). These findings are similar to those of Gilka *et al* (17) who investigated the potential importance of edema in the pathogenesis of pneumonic pasteurellosis. An early bronchiolitis was present subsequent to challenge with *P. hemolytica*. Polymorphonuclear leukocytes were consistently present in the bronchiolar tissue and in the peribronchiolar and peripheral alveolar septa. They also demonstrated early occurrence of minute areas of peribronchiolar and peripheral atelectasis, probably due to the removal of alveolar lining film. Alveolar macrophage was the principal cell of phagocytosis and polymorphonuclear leukocytes also participated in the process to some extent but not the large alveolar epithelial cells.

Friend *et al* (13) found, in later stages, generalized distention of lymphatic vessels with fibrin and neutrophils. Gilka *et al* (17) consistently found widely dilated lymphatics in close proximity to the atelectatic areas. They postulated that edema fluid might have removed the alveolar surfactant material into these adjacent lymphatics resulting in subsequent collapse of the alveoli.

In the more characteristic late experimental lesions (13), the findings of acute bronchiolitis, with presence of large number of pale eosinophilic macrophages, neutrophils and homogenous eosinophilic clots of fibrin in alveoli and alveolar ducts were consistent with natural lesions. The presence of small areas of coagulation necrosis, irregular in size and shape, many progressing into liquefaction necrosis, is similar to natural cases of pasteurellosis (29) and some cases of contagious bovine pleuropneumonia (5). Characteristic fusiform elongate dark basophilic streaming macrophages around these lesions also occurred in alveoli unassociated with necrotic tissue and thrombosis of the lymphatic vessels was common (13).

The histological description of late stages of the lesion of experimental (13) and field cases (29, 40) considered so characteristic for pneumonic pasteurellosis, was not encountered in any of the other spontaneous or experimental cases of "shipping fever" reviewed.

A comparable description of the characteristic lesions with areas of coagulation necrosis, was encountered in reports of lesions observed in experimental infections with other agents in pigs. Shope (43) in describing experimental *H. parahemolyticus* infection, refers to subgross examination of the necrotic areas as bizarre designs, circles, bands and irregularly shaped areas that were discretely outlined along their margins by more deeply staining tissue components. Hani *et al* (21) in their description of experimental and spontaneous cases of porcine *H. parahemolyticus* pleuropneumonia, mentioned the presence of round, polygonal or fusiform cells with strikingly basophilic nuclei, which proliferate and desquamate into alveolar lumina early in the course of the disease.They described capillary congestion, alveolar and interlobular edema, hemorrhage, intravascular fibrinous thrombosis and focal necrosis in peracute cases. In their experimental *S. choleraesuis* pneumonia in pigs, Baskerville and Dow (2) observed the lung lesions at different stages of severity. They found necrosis of a number of interalveolar septa which led to aggregation of adjacent masses of degenerating cells with the formation of a characteristic pattern of deeply basophilic whorls. As the disease progressed, they noted presence of "widespread necrosis and abscess formation in which only "ghost" tissue remained and the necrotic areas were clearly demarcated from the healthy tissue by a zone of polymorphonuclears and by fibroblasts arranged in parallel layers".

Bygrave *et al* (5) studied lung lesions in various stages of severity in an outbreak of contagious bovine pleuropneumonia. In their comments regarding the sequestrated lesions in chronic cases, they stated that "necrosis of the lobules developed secondarily to thrombosis of the intralobular and interlobular arteries". They further stated that one lobule or part of the lobule became necrotic when intralobular vessels were thrombosed, while multiple lobules became necrotic when interlobular vessels were thrombosed.

## DISCUSSION

This paper originates from a laboratory where work on the pathogenetic mechanisms of pneumonic pasteurellosis has been conducted for some time, and in which the lesions have always been of interest. The gross lesions of acute fibrinous pneumonia in acute untreated fatal natural cases are very characteristic and well known. The lesions in nonfatal natural cases are less well known and are the subject of a paper in preparation. The areas of coagulation necrosis are also very characteristic, but their pathogenesis is not clear. Suggestions of infarction have not been verified. The same type of microscopic lesion occurs in acute fatal cases of *P. hemolytica* infection in sheep and goats (29) as well as in natural cases of *H. parahemolyticus* induced fibrinous pneumonia and experimental salmonellosis in pigs. The lesion may well have a common pathogenesis in each of these cases.

Work in this laboratory indicates that *P. hemolytica* can induce the lesion by itself experimentally, but it is clear that PI-3 virus infection as well as IBR virus infection may facilitate the establishment of *P. hemolytica* in the lung in appropriate amounts to induce the fibrinous pneumonia. There may well be other agents, viral, chlamydial or mycoplasma, that could facilitate the establishment of *P. hemolytica* in the lung. The facilitators interfere with normal pulmonary clearance mechanisms which are trying to dispose of increased numbers of bacteria as a result of their marked build-up in the nasal flora (50). Current work suggests that live *P. hemolytica* organisms are required in the lung in large numbers for lesions to develop. Little is known about host resistance to the disease, either natural or induced, or immune mechanisms which induce resistance, but this area of investigation is now being actively explored (33).

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## LETTER TO THE EDITOR

### The Present Status of Euthanasia by Nonanesthetic Gases

DEAR SIR:

The nonanesthetic gases that are used or have been used in euthanasia, either singly or in combination with other agents include: carbon monoxide, carbon dioxide, nitrogen, argon and cyanide. They may be combined with anesthetic gases such as: chloroform, carbon tetrachloride, carbon disulfide, halothane, fluorane and methoxy-fluorane. Combination of these nonanesthetic gases with anesthetic gases makes their use more acceptable, providing the lag phase is without distressful signs in the animals being destroyed.

Although the nonanesthetic gases are widely used and have been acclaimed by numerous animal welfare agencies such as the American Humane Association (carbon monoxide, nitrogen), the Universities Federation for Animal Welfare and some affiliates of the Canadian Federation of Humane Societies, controversy is developing concerning their acceptability (3,4).

In theory, the replacement of the air by these nonanesthetic gases produces a deficiency of available oxygen and the animal develops brain anoxia. Without sufficient oxygen, the brain becomes depressed and the animal lapses into unconsciousness.

A close examination of the hypoxic methods reveals that the dog or cat shows certain behavioral and physical changes during the period before collapse, unconsciousness and death occur. Examination of the animal during vocalization associated with nitrogen flushing has revealed the persistence of a blinking reflex. Although some claim (1) that during this stage the animal is disoriented, confused and does not feel pain, the controversial state is that the dog in a chamber with a concentration of 1.5% oxygen, vocalizes and possesses a strong blinking reflex. Within 15 to 20 seconds, when this dog is exposed to air, with the oxygen concentration reaching 10-12% in the chamber, the animal will stand on its feet without staggering, possessing normal behavioral responses to human touch and voice. The recovery is so rapid that it is difficult to accept that the animal has been in a confused, disoriented state and incapable of experiencing pain (2). In human studies they are not exposed to the rapid hypoxic state produced during euthanasia of unwanted dogs and cats. During the lag phase the dog or cat may experience such rapid lack of oxygen that death by suffocation or asphyxiation results.

These nonanesthetic gases for euthanasia require additional research before they can be accepted as fulfilling the criteria of a humane method for euthanasia. Furthermore, they should not be used on newborn puppies or kittens, for these animals have been accustomed to low oxygen levels in the uterus and are resistant to hypoxic conditions.

The humane destruction of unwanted newborn puppies and kittens may be carried out by the use of intracardial injections of a barbiturate or T-61. In our laboratory we have observed the intraperitoneal injection of T-61 in the newborn to produce a humane, rapid death without pain or distress. However, in the adult animal or puppies and kittens more than ten days old only the intravenous or intracardiac route for T-61 can be recommended.

It is cautioned that any injectable drug can cause unnecessary pain and suffering if the individual carrying out the technique has not been properly selected or trained.

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